JOURNAL OF VIRAL HEPATITIS
JVH

Journal of Viral Hepatitis, 2015, **22**, (Suppl. S1), 26–45 doi:10.1111/jvh.12351

The present and future disease burden of hepatitis C virus (HCV) infections with today's treatment paradigm – volume 2

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SUMMARY. Morbidity and mortality attributable to chronic hepatitis C virus (HCV) infection are increasing in many countries as the infected population ages. Models were developed for 15 countries to quantify and characterize the viremic population, as well as estimate the number of new infections and HCV related deaths from 2013 to 2030. Expert consensus was used to determine current treatment levels and outcomes in each country. In most countries, viremic prevalence has already peaked. In every country studied, prevalence begins to decline before 2030, when current treatment levels were held constant. In contrast, cases of advanced liver disease and liver related deaths will continue to increase through 2030 in most countries. The current treatment paradigm is inadequate if large reductions in HCV related morbidity and mortality are to be achieved.

Keywords: diagnosis, disease burden, epidemiology, HCV, hepatitis C, incidence, mortality, prevalence, treatment.

INTRODUCTION

Globally, there are an estimated 115 million anti-HCV-positive individuals and 80 million viremic hepatitis C virus (HCV) infections [1], and the HCV disease burden has been increasing [2,3]. Between 1990 and 2010, the total HCV liver related mortality increased by 50% [4]. National studies have also shown an annual increase in the number

Abbreviations: G, Genotype; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IDU, injection drug use; MSM, men who have sex with men; Peg-IFN, pegylated interferon; PI, protease inhibitor; RBV, ribavirin; SMR, standard mortality ratio; SVR, sustained viral response.

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of hepatocellular carcinoma (HCC) cases and liver transplants due to HCV [5–7]. However, annual HCV-related disease burden data are not available in all countries. Robust estimates of HCV-related mortality and morbidity (numbers and trends) are needed to help policymakers develop strategies to tackle the rising disease burden.

Models have been used to forecast the progression of liver disease and to estimate the total burden and changes in HCV sequelae over time [2,8–14]. In countries with available data, the disease progression rates were back-calculated to fit reported cases, and the model was used to forecast future trends. This allowed for comparison of different intervention strategies and their relative impact on future disease burden.

Although the methodologies were similar in different modelling studies, comparison of change in HCV disease burden across multiple countries could best be assessed if the same model and approach were used. The aim of this study was to estimate the total number of HCV infections, new infections, diagnosed, treated and cured as well as mortality and treatment protocols in 2013. HCV epidemiology data are often reported in different years, and a mathematical model can be used to estimate the HCV-infected populations in a given year, allowing for comparison across countries. The second goal of this study was to estimate the future disease burden (2013–2030) if the current treatment paradigm and response rate continued, and to compare the results across different countries. This analysis is consistent with previously published work [8] to allow for comparison of results across all the countries assessed so far.

METHODOLOGY

Inputs

The historical epidemiology of HCV was gathered through a literature search, analysis of unpublished data and discussion with expert panels [15]. When no input data were available, analogues (data from countries with a similar healthcare practice and/or risk factors) or expert inputs were used. Ranges were used to capture uncertainty in inputs with wider ranges implying greater uncertainty.

Model

A disease progression model was constructed in Microsoft Excel® (Microsoft Corp., Redmond, WA, USA) to quantify the size of the HCV-infected population, by the liver disease stages, from 1950 to 2030. Microsoft Excel was selected as a platform due to its transparency, availability and minimal need for operator training. The model was set up for sensitivity and Monte Carlo analysis using Crystal Ball®, an Excel® add-in by Oracle®. Beta-PERT distributions were used for all uncertain inputs. The Excel® optimization add-in, Frontline Systems' Solver, was used to calculate the number, age and gender distribution of the annual acute infections.

The model has been previously described in detail [8]. It started with the annual number of acute infections that progressed to chronic HCV (viremic) infection after accounting for spontaneous clearance of the virus (Fig. 1). The progression of these new cases was followed along with all chronic infections from prior years. Unless specified, the scope of the model was limited to viremic, HCV ribonucleic acid (RNA)-positive cases. Nonviremic cases (those who spontaneously cleared the virus or were treated and cured) were not considered even though they would test positive to HCV antibodies and may still progress to more advanced stages of liver disease despite viral clearance [16]. The total number of cases, at each stage of the disease, was tracked by age and gender. Five-year-age cohorts were used through age 84, and those aged

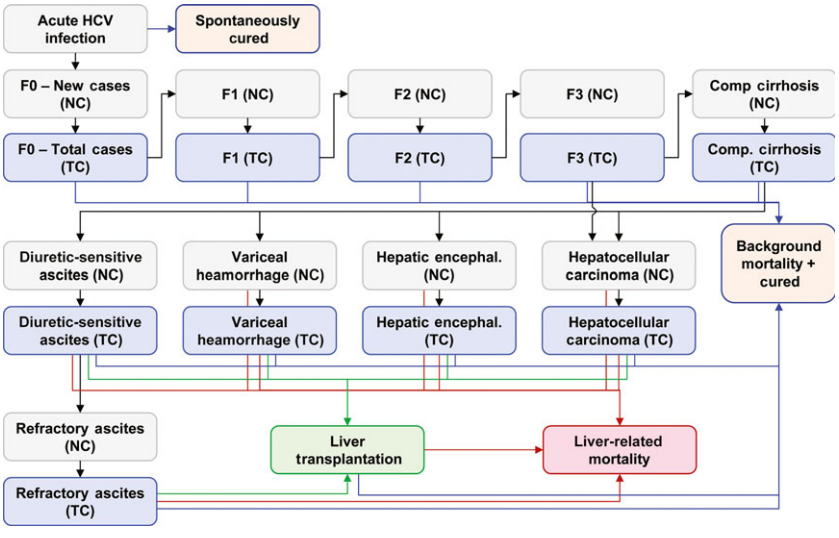

Fig. 1 The flow of the hepatitis C virus (HCV) disease progression model.

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85 and older were treated as one cohort. Each year, one-fifth of the population in each age group, except for 85 and older, was moved to the next age cohort to simulate ageing.

The historical number of HCV infections, and the age and gender distributions were gathered through a literature search and discussions with an expert panel [15]. These data were used to estimate the historical number of new HCV infections as described below.

New HCV Infections & Re-infection

When available, reported or calculated annual estimates of new infections were used. In most countries, the number of new HCV infections was not available and was back-calculated. At any point in time, the total number of HCV infections equals the sum of all new infections minus the number of spontaneously cleared, deceased and cured cases.

The number of new infections was back-calculated using a two-step process that first calculated the annual number of new cases, followed by the age and gender distribution of these cases. The annual number of new cases was calculated using the known number of total HCV infections in a given year in a country. The model calculated the annual number of all-cause mortality, liver related deaths and cured cases as described below. The Excel® optimization add-in, Solver, was used to determine an average number of new infections per year. However, the annual number of new cases did not remain flat since 1950. Thus, an annual relative incidence value was used to describe the change in the number of new infections over time. Relative incidence was set to one in 1950, and a discussion with the expert panel was used to identify the years when new infections peaked using the risk factors common in the country (nosocomial infections, injection drug use, etc.).

When immigration from endemic high-risk countries was highlighted as an important source of new infections, the annual number of new cases due to immigration was calculated by gathering net annual immigration, by country of origin and from national databases regarding the anti-HCV prevalence in the country of origin.

In the second step, the age and gender of the acute infections were calculated using the age and gender distribution of the total infected population in a given year. The Excel® optimization add-in, Frontline Solver, was used to back-calculate the age and gender distributions of the new infections in 1966 and every 5 years thereafter until the year of known distribution in the total infected population. The age and gender distribution in years 1950–1965 were set to equal 1966 and trended linearly between the 5-year increments.

It was assumed that in the absence of better information, future HCV infection and re-infection will remain the same as they are today. This is a more conservative approach than a dynamic model, which would show a reduction in HCV incidence with treatment of high-risk populations (treatment as prevention). This conservative approach was deemed appropriate given the uncertainties present for HCV epidemiology and lack of detailed data on infection and re-infection rates.

Progression rates

Disease progression was simulated by multiplying the total number of cases at a particular stage of the disease by a progression rate to the next stage. The rates were gathered from previous studies [2,9,17–23] or calculated using known number of HCC cases/ mortality as explained previously [8].

The number of new cases at a stage of the disease was calculated by multiplying the progression rate and the total number of cases at the previous stage of the disease in the previous year. The total number of cases was adjusted for ageing, all-cause mortality and cured in any given year.

All-cause mortality

The all-cause mortality rates by age and gender were gathered from the Human Mortality Database [24] unless stated otherwise. The rates were adjusted for incremental increase in mortality due to injection drug use (IDU) and transfusion, as described previously [25]. Unless specified, a standard mortality ratio (SMR) of 10 (9.5–29.9) was used for the portion of the HCV-infected population who were active IDU between ages 15 and 44 [26–31]. An SMR of 2.1 (1.3–17.6) was applied to all ages for the portion of the population infected due to transfusion [32]. In all countries studied, new HCV infections due to transfusion were no longer a risk factor. A linear declining rate was applied to get the percentage of total infections attributed to transfusion to zero by 2030. The adjustments to all-cause mortality for active IDU and transfusion were made using the following assumptions:

Argentina

In 2001, 9.3% of the population was active IDU. This percentage was back-calculated using estimates of 65 000 IDU in Argentina [33], and an IDU HCV prevalence of 54.6% [34]. Based on results from a national study, it was assumed that 20.8% of the infected population was infected through transfusion in 2005 [35].

Finland

In 2012, it was estimated that transfusion accounted for 0.6% of the transmission of HCV infection [36], whereas it was estimated by an expert panel that active IDU accounted for 60% of the transmission.

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Greece
From 1997-2006, IDU was reported as a risk factor in 30.7% of patients, whereas transfusion prior to 1992 was reported as a risk factor in 22.6% of patients [37]. It was estimated that 11% of the total infections were active IDU [38].

India
In 2006, it was estimated that transfusion accounted for 4.8% of the transmission of HCV [39], with approximately 6.5% occurring through IDU [40]. Additionally, an estimated 1/3 of new cases were due to unsafe medical injections, with approximately 1.8 billion unsafe injections occurring annually.

Ireland
In 2003, 20.1% of the population was active IDU. This percentage was back-calculated using estimates of 10 110 IDU in Ireland [33], and an IDU HCV prevalence of 74.6% [34]. A national study reported that 79.7% of HCV infected cases report drug use as a risk factor, but this includes individuals who have not used drugs recently [41]. In Ireland, a national study estimated that 16.4% of the population was infected through transfusion in 2004 [41].

Israel
In 2004, it was estimated that 3.7% of the HCV population was active IDU. There were approximately 9000 active IDU in Israel in 2004, with an estimated seroprevalence of 40% (personal communication with P. Roska, 2014). An estimated 38% of transmissions occurred through transfusion, with 42% among native Israelis and 11.7% among immigrants [42,43].

Luxembourg
In 2006, it was estimated that 71.4% of the HCV-infected population acquired their infection through IDU [44]. In 2012, there were 2500 active IDU in Luxembourg, with approximately 70% HCV seroprevalence (Expert consensus). This corresponds with approximately 43.75% active IDU among the HCV-infected population.

Mexico
Transfusion prior to blood screening is the predominant risk factor for chronic HCV infection. In a study of patients from 2006 to 2009, transfusion was listed as a risk factor for 60.8% of individuals [45]. It was estimated in 2008 that IDU accounted for 2.5% of HCV infections [46].

Mongolia
Based on expert consensus, it was estimated that 0.5% of the infected population were active IDU in 2013. Based on results from a Taiwanese study, it was assumed that 26.8% of the infected population was infected through transfusion [47].

The Netherlands
Historical risk factor data were available from an analysis of acute and chronic HCV infections reported to the national notification system from April 1999 to February 2001. Acute infections accounted for 6% of the sample [48]. In this report, it is estimated that transfusion accounted for 6% of the transmission of HCV infection, and past or present IDU accounted for 64% of transmission [48]. However, due to the current unpopularity of injecting, as well as an effectively implemented clean needle exchange programme, it was estimated that only six individuals were infected through IDU in 2013. The largest risk groups for HCV in the Netherlands are believed to arise from first-generation migrants from HCV endemic countries and HIV-positive men who have sex with men (MSM) [49].

New Zealand
Based on expert consensus, it was estimated that approximately 1% of the New Zealand population were active IDU, of whom 30% were infected with HCV. Based on these data, it is estimated that 20.2% of the total infected population are active IDU, while previous research shows that 82.8% of infected cases report a history of IDU [50]. A national study reported that 3.8% of the viremic population was infected through transfusion [50].

Norway
In 2012, it was estimated that 90% of the HCV-infected population acquired their infection through IDU (personal communication with Olav Dalgard, 2014). Among those infected, it was estimated that one-third were active users. Additionally, in 2000, it was shown in a population-based prevalence study that 1.5% of those with HCV had acquired the infection through transfusion before 1990 (personal communication with Olav Dalgard, 2014).

Poland
It is estimated, from 1998 to 2001, that transfusion accounted for 9% of the transmission of HCV infection [51], whereas, in 2013 it was estimated that 5% of the viremic population were active IDU.

Russia
It was estimated in 1995 that prior transfusion was a risk factor for 26% of anti-HCV positive persons [52], whereas 13% of individuals with HCV reported drug addiction as a risk factor [52]. According to expert consensus, the percentage of the population injecting has remained fairly constant. It was estimated that 16% of the HCV-infected population were IDU.

Slovak Republic
It is estimated in 2005 that prior transfusion accounted for 31% of the transmission of HCV infection [53], whereas in

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2006 it was estimated that 55% of individuals with HCV reported past or present IDU as a risk factor [54]. In 2013, it was estimated that 18% of the infections were among active IDU.

South Africa

There were little data available on risk factors in South Africa. It was estimated that 10–15% of the population living with HCV were active IDU and that 20% of the population were infected through transfusion prior to 1990. There have been no reported cases of HCV transmission since 2005 (personal communication with M Vermeulen, 2014).

Diagnosed

The total number of diagnosed cases was collected and reported previously [15]. To estimate current and future total diagnosed cases, it was assumed that the number of newly diagnosed cases stayed the same as the last reported year.

Treated & cured

As described previously [15], analysis of pegylated interferon (Peg-IFN) or ribavirin (RBV) units sold, or national data, were used to estimate the total number of treated HCV patients. It was assumed that the number of treated patients stayed constant after the last reported year. It was also assumed that the number of treated patients for each genotype was proportional to the genotype distribution of the HCV-infected population [15].

The annual number of cured patients was estimated using the average sustained viral response (SVR) rate in a given year. A separate SVR was used for the major genotypes, as shown in Table 1. Different methods were used to estimate the average SVR. All countries took into consideration a weighted average of different treatment options in a given year – interferon-based therapy in combination with RBV (dual therapy) or with RBV and a protease inhibitor (PI) (triple therapy). Some also took into consideration the percentage of the population who were treatment experienced and treatment naïve on each treatment option, while other countries took into account the disease stages of the patients being treated (e.g., F1, F2, F3 and F4).

The number of cured patients from all genotypes was summed by stage of the disease and distributed proportionally among age eligible cohorts (see below). If the treatment protocols in a country recommended treatment of patients aged 20–69, the number of cured patients was distributed based on the number of infected individuals in each cohort between ages 20–69, and it was assumed that no one younger than 20 or older than 69 was treated and cured.

Treatment protocols

The pool of patients who could be treated was impacted by explicit or implicit treatment protocols. Explicit protocols were determined by national or international guidelines, whereas implicit protocols were determined by actual practice in the country. In 2013, decompensated cirrhotic patients were considered ineligible in all countries.

According to the literature, approximately 40–60% of HCV patients are eligible for Peg-IFN/RBV [55,56]. The definition of eligibility included contraindications to the drugs (e.g., psychiatric conditions) as well as patient's preference. In this analysis, 20–65% of the patients were considered treatment eligible for standard-of-care (Table 1). The standard-of-care varied across countries and genotypes. High and low SVR rates for genotype 1 (Table 1) were indicative of availability of triple therapy (Peg-IFN + RBV + PI). High SVR rates were observed when triple therapy was made available to early-stage genotype 1 patients, while low SVR rates were observed when triple therapy was restricted to patients with late-stage liver disease. The numbers reported here represent a weighted average of all patients and therapies.

In each country, the expert panel provided the most common stages of fibrosis considered for treatment (Table 1). Many countries use, or are starting to use, non-invasive testing methods to determine the level of fibrosis on patients. However, the Metavir scale was used in this model to represent the severity/stage of liver fibrosis. The age of the patients was also considered. Table 1 outlines the most common age bands considered for treatment. The data presented here do not imply that patients with lower Metavir score or older/younger patients were not treated in each country. Instead, the data provided a range for the majority of treated patients.

Future treatment protocols

In this analysis, it was assumed that the future treatment paradigm will remain the same as today. Thus, all assumptions (the number of acute cases, treated patients, percentage of patients eligible for treatment, treatment restrictions, the number of newly diagnosed annually and the average SVR by genotype) were kept constant in future years.

RESULTS

The results of the analysis for 2013 are shown in Table 1. Figure 2 shows the age distribution of the HCV-infected population by country. Table 2 compares the change in HCV disease burden in 2013 and 2030, while Figs 3 and 4 show the projected HCV disease burden between the years 1950 and 2030. It should be noted that decompensated cirrhosis figures excluded those who received a liver transplant.

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Table 1 Hepatitis C virus (HCV)-infected population and treatment forecasts in 2013

	Argentina	Finland	Greece	India	Ireland	Israel	Luxembourg	Mexico
Country's population (000)	41 500	5600	11 400	1 275 100	4600	7800	500	117 500
Total viremic infections (000)	342 (155 - 537)	22 (16 - 25)	133 (57 - 179)	8666 (4623 - 14 331)	30 (27 - 30)	105 (41 - 108)	3.1 (1.9 - 3.4)	561 (327 - 605)
Viremic prevalence (%)	0.83% (0.37% - 1.29%)	0.39% (0.29% - 0.45%)	1.16% (0.50% - 1.56%)	0.68% (0.36% - 1.12%)	0.65% (0.59% - 0.65%)	1.34% (0.53% - 1.38%)	0.58% (0.37% - 0.64%)	0.48% (0.28% - 0.52%)
Total diagnosed (viremic)								
Total cases	116 800	16 400	34 700	430 500	11 600	25 100	2600	170 900
Annual newly diagnosed	4900	900	4000	52 600	800	2200	100	14 700
Diagnosis rate (%)	34%	75%	26%	5%	38%	24%	84%	30%
Newly diagnosed rate (%)	1.4%	4.3%	3.0%	0.6%	2.7%	2.1%	3.2%	2.6%
Treated & cured								
Annual number treated	650	300	1970	15 000	250	1010	100	3110
Annual number cured	420	220	1420	10 390	200	650	70	1780
Average SVR (%)	65%	73%	72%	69%	78%	64%	70%	57%
Treatment rate (%)	0.2%	1.4%	1.5%	0.2%	0.8%	1.0%	3.2%	0.6%
New infections								
Total cases	1950	640	3700	287 920	660	100	110	5620
Infection rate (per 100K)	5	11	32	23	14	1	21	5
Risk factors								
Number of active IDU	31 950	13 110	14 240	563 310	6410	3870	1350	14 020
% Active IDU	9%	60%	11%	6%	21%	4%	44%	3%
Previous blood transfusion	48 420	120	21 310	294 660	3170	14 210	0	275 970
% Previous blood transfusion	14%	1%	16%	3%	10%	14%	0%	49%
Mortality								
All cases	8050	260	3670	150 970	220	1680	25	14 690
All cause mortality	6500	210	2900	136 460	180	1240	20	12 320
Liver related mortality	1550	50	770	14 510	40	440	5	2370
Current treatment protocols								
Treatment age	15 - 69	20 - 64	30 - 69	15 - 69	15 - 64	20 - 64	15 - 69	20 - 69
% Treatment eligible	60%	60%	60%	60%	60%	60%	60%	60%
Treated stages - G1	>= F3	>= F2	>= F0	>= F0	>= F2	>= F2	>= F2	>= F2
Treated stages - G2	>= F2	>= F2	>= F0	>= F0	>= F2	>= F0	>= F2	>= F2
Treated stages - G3	>= F2	>= F2	>= F0	>= F0	>= F2	>= F0	>= F2	>= F2
Treated stages - G4	>= F2	>= F2	>= F0	>= F0	>= F2	>= F2	>= F2	>= F2
SVR - G1 (%)	60%	50%	70%	62%	76%	64%	75%	50%
SVR - G2 (%)	75%	85%	90%	67%	90%	80%	70%	80%
SVR - G3 (%)	65%	85%	75%	67%	76%	60%	80%	60%
SVR - G4 (%)	75%	70%	65%	62%	48%	45%	40%	50%

(continued)

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Table 1 *(continued)*

	Mongolia	Netherlands	New Zealand	Norway	Poland	Russia	Slovak Republic	South Africa
Country's population (000)	2900	16 800	4500	5000	38 300	142 600	5500	51 000
Total viremic infections (000)	200	20	50	22	200	4525	33	393
	(136 - 245)	(5 - 36)	(30 - 63)	(15 - 27)	(141 - 234)	(3168 - 4675)	(22 - 41)	(238 - 475)
Viremic prevalence (%)	6.8%	0.12%	1.11%	0.43%	0.52%	3.17%	0.60%	0.77%
	(4.6% - 8.4%)	(0.03% - 0.22%)	(0.67% - 1.40%)	(0.30% - 0.53%)	(0.37% - 0.61%)	(2.22% - 3.28%)	(0.40% - 0.75%)	(0.47% - 0.93%)
Total diagnosed (viremic)								
Total cases	60 000	12 000	20 000	12 600	29 900	1 807 900	3300	55 500
Annual newly diagnosed	1300	700	900	1100	3000	55 900	300	2600
Diagnosis rate (%)	30%	61%	40%	57%	15%	40%	10%	14%
Newly diagnosed rate (%)	0.6%	3.3%	1.8%	5.0%	1.5%	1.2%	0.8%	0.7%
Treated & cured								
Annual number treated	200	880	900	610	4040	5500	320	100
Annual number cured	130	610	570	370	1790	3060	160	70
Average SVR (%)	65%	69%	63%	61%	44%	56%	50%	70%
Treatment rate (%)	0.1%	4.5%	1.8%	2.8%	2.0%	0.1%	1.0%	0.0%
New infections								
Total cases	3030	510	1020	750	5460	236 090	760	6940
Infection rate (per 100K)	103	3	23	15	14	166	14	14
Risk factors								
Number of active IDU	1000	4210	10 340	6570	9980	723 970	6060	47 140
% Active IDU	0%	21%	21%	30%	5%	16%	18%	12%
Previous blood transfusion	28 480	670	1790	310	10 530	571 420	6980	0
% Previous blood transfusion	14%	3%	4%	1%	5%	13%	21%	0%
Mortality								
All cases	5400	480	590	240	4030	77 010	770	19 970
All cause mortality	4270	380	450	190	3360	71 900	640	18 420
Liver related mortality	1130	100	140	50	670	5110	130	1550
Current treatment protocols								
Treatment age	40 - 59	15 - 69	15 - 59	15 - 64	20 - 69	15 - 64	15 - 64	15 - 69
% Treatment eligible	60%	60%	60%	60%	80%	60%	60%	60%
Treated stages - G1	>= F2	>= F1	>= F0	>= F2	>= F1	>= F1	>= F2	>= F1
Treated stages - G2	>= F2	>= F1	>= F0	>= F2	>= F1	>= F1	>= F2	>= F1
Treated stages - G3	>= F2	>= F1	>= F0	>= F2	>= F1	>= F1	>= F2	>= F1
Treated stages - G4	>= F2	>= F1	>= F0	>= F2	>= F1	>= F1	>= F2	>= F1
SVR - G1 (%)	65%	50%	60%	42%	40%	50%	48%	70%
SVR - G2 (%)	80%	80%	80%	80%	75%	75%	70%	90%
SVR - G3 (%)	66%	70%	65%	75%	70%	60%	70%	75%
SVR - G4 (%)	40%	50%	50%	42%	40%	50%	48%	65%

Viremic infections – active HCV infections who are RNA positive, viremic prevalence – prevalence of active HCV infections, viremic diagnosed – the number individuals diagnosed with an active infection, annual newly diagnosed – the number of active (viremic or RNA positive) HCV infections diagnosed for the first time, diagnosis rate – total viremic diagnosed cases divided by total viremic infections, newly diagnosed rate – number of new viremic diagnosed cases divided by total viremic infections.

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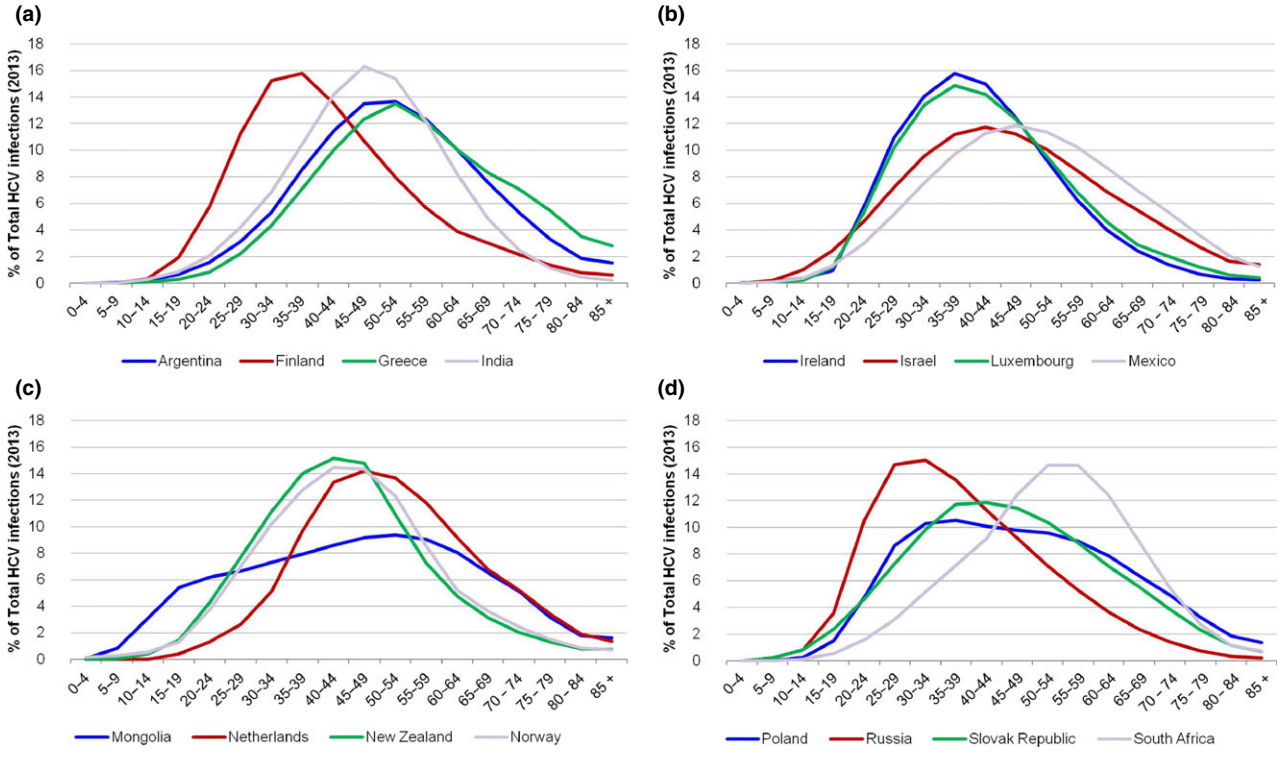

Fig. 2 Distribution of the 2013 hepatitis C virus (HCV)-infected population by age as a percentage of total number of cases.

Argentina

Based on expert consensus, historical changes in incidence were estimated. It was estimated that peak incidence occurred in 1989 and has since decreased with blood screening. In 2013, it is estimated that 1950 new infections occurred in Argentina.There were an estimated 342 300 (155 000–537 000) infected individuals in 2013. Prevalence is estimated to have peaked at 382 700 patients in 2002 and to decline to 237 000 by 2030. There will be 62 630 compensated cirrhotic patients in 2030 as compared to 37 110 in 2013. In addition, there will be 3510 cases of HCC, and 8470 patients progressed to decompensated cirrhosis by 2030. Liver related deaths in 2030 will number 3060 as compared to 1550 deaths in 2013. In 2013, 13% of viremic cases are estimated to have compensated cirrhosis or more advanced liver disease (decompensated cirrhosis, HCC or transplant), while this proportion will increase to 32% in 2030.

Finland

The annual number of reported HCV infections peaked in Finland in 1997, with approximately 1900 cases [36]. The number of cases reported decreased through 2009 and has remained stable, with 1000–1200 annual cases reported. There were limited data available on the number of new cases of HCV in Finland. The annual number of new cases was estimated at 640 new cases in 2013.

In 2013, the total number of viremic infections was estimated at 21 800 (16 000–25 200), and it was forecasted to remain relatively constant, with 21 800 viremic infections in 2030. The number of HCC cases in 2013 was estimated at 50 cases, and it was forecasted to double by 2030. The number of liver related deaths will increase by 80% from a base of 50, while decompensated cirrhosis and compensated cirrhosis infections will increase 65% and 95% from a base of 120 and 960 in 2013.

Greece

Relative incidence was estimated using previously published data from 1950 to 1990 [11]. The number of new infections peaked in 1990, and it was estimated to have decreased by 50% to date. There were an estimated 3700 new cases of HCV in Greece in 2013.

In 2013, the total number of viremic infections was estimated at 133 000 (57 200–179 000), and it was forecasted to decrease to 106 700 viremic infections in 2030. The number of HCC cases in 2013 was estimated at 910 cases, and it was forecasted to increase by 35% by 2030. The number of liver related deaths will increase by 35% from a base of 770, while decompensated cirrhosis and

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Table 2 Comparison of hepatitis C virus (HCV) disease burden in 2013 and 2030

	Argentina	Finland	Greece	India	Ireland	Israel	Luxembourg	Mexico	Mongolia	Netherlands	New Zealand	Norway	Poland	Russia	Slovak Republic	South Africa
Viremic HCV Infections (000)																
2013 Est.	342	22	133	8666	30	105	3.1	561	200	20	50	22	200	4525	33	393
2030 Est.	237	22	107	8413	29	68	2.8	406	165	10	40	21	185	6164	29	219
Percent Change	(30%)	0%	(20%)	(5%)	(5%)	(35%)	(10%)	(30%)	(15%)	(50%)	(20%)	(5%)	(5%)	35%	(10%)	(45%)
HCC Cases																
2013 Est.	1740	50	910	14 090	40	460	4	2660	1200	100	140	50	780	5170	130	1610
2030 Est.	3510	90	1220	56 800	160	880	7	4150	1520	90	370	100	1170	16 530	190	2050
Percent Change	100%	100%	35%	305%	360%	90%	75%	55%	25%	0%	155%	115%	50%	220%	50%	30%
Liver Related Mortality																
2013 Est.	1550	50	770	14 510	40	440	4	2370	1130	100	140	50	670	5110	130	1550
2030 Est.	3060	80	1030	53 520	150	790	5	3630	1400	80	340	80	1020	16 100	180	2010
Percent Change	95%	80%	35%	270%	315%	80%	25%	55%	25%	(25%)	140%	80%	50%	215%	40%	30%
Decompensated Cirrhosis																
2013 Est.	4460	120	2190	52 530	60	1440	11	6750	3660	250	420	90	1580	17 140	390	4810
2030 Est.	8470	200	2830	165 510	190	2370	10	10 560	4330	140	960	110	2240	51 960	510	5660
Percent Change	90%	65%	30%	215%	220%	65%	(10%)	55%	20%	(45%)	130%	20%	40%	205%	30%	20%
Compensated Cirrhosis																
2013 Est.	37 110	960	17 230	448 710	970	10 400	90	54 460	25 930	2270	3300	990	16 000	145 330	2900	40 500
2030 Est.	62 630	1870	19 810	1 202 160	3420	16 120	120	76 400	27 540	1350	7460	1870	21 190	399 130	3820	39 710
Percent Change	70%	95%	15%	170%	255%	55%	30%	40%	6%	(40%)	125%	90%	30%	175%	30%	0%

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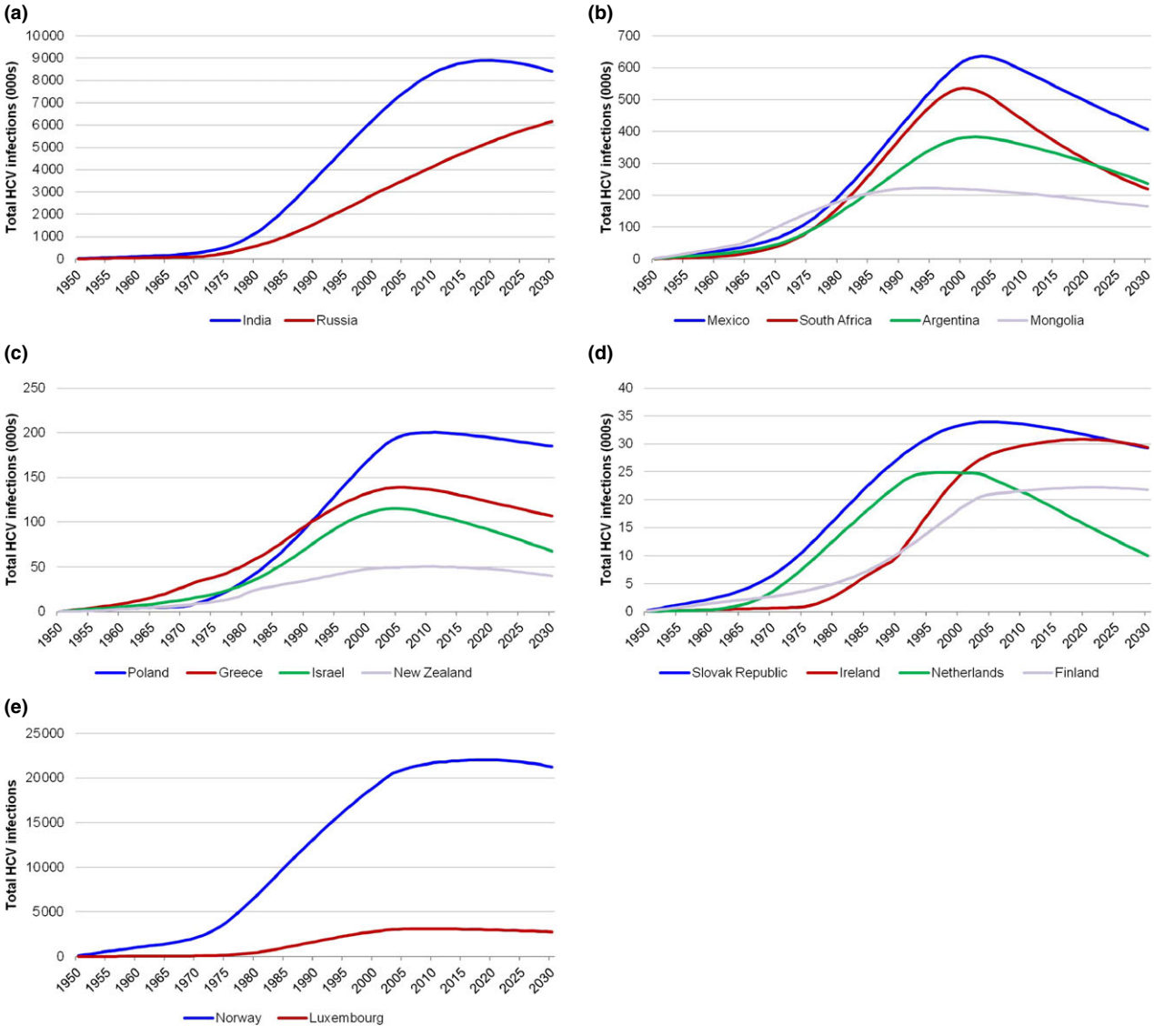

Fig. 3 Change in viremic hepatitis C virus (HCV) infections over time.

compensated cirrhosis infections will increase 30% and 15% from a base of 2190 and 17 200 in 2013.

India

Expert consensus suggests that unsafe injection procedures contribute most heavily to the transmission of HCV in India. While the annual number of new cases of HCV was estimated to peak in 2001, prior to blood screening, incidence remains high due to unsafe injection practices. Approximately 1/3 of new cases were thought to result from unsafe injections, and it was estimated that 1.8 billion injections each year were unsafe. In 2013, there were approximately 287 920 new infections (23 cases per 100 000 persons).

It is estimated that there were 8 666 300 (4 622 700–14 331 200) viremic infections in 2013. Viremic infections were estimated to peak at 8 901 500 in 2019 before declining to 8 412 500 in 2030. The number of HCC cases in 2013 was estimated at 14 090 cases, and it was forecasted to increase by 305% by 2030. The number of liver related deaths was forecasted to increase by 270% from a base of 14 510, while decompensated cirrhosis and compensated cirrhosis infections were forecasted to increase 215% and 170% from a base of 52 530 and 448 710 in 2013. In 2013, an estimated 6.0% of the viremic population experienced cirrhosis, decompensated cirrhosis, HCC or liver transplant. By 2030, this proportion was projected to increase to 17.0%.

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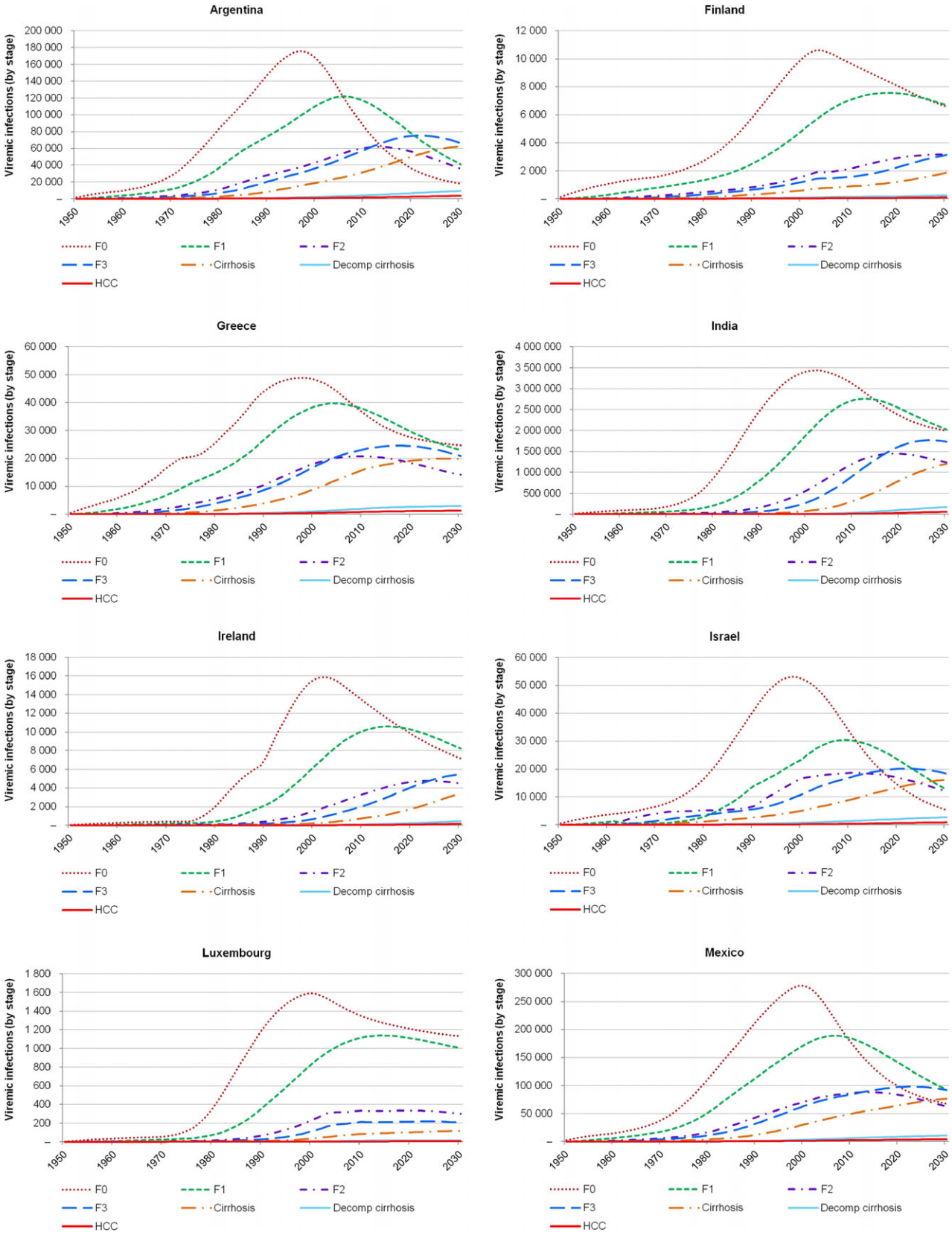

Fig. 4 Change in hepatitis C virus (HCV) disease burden over time.

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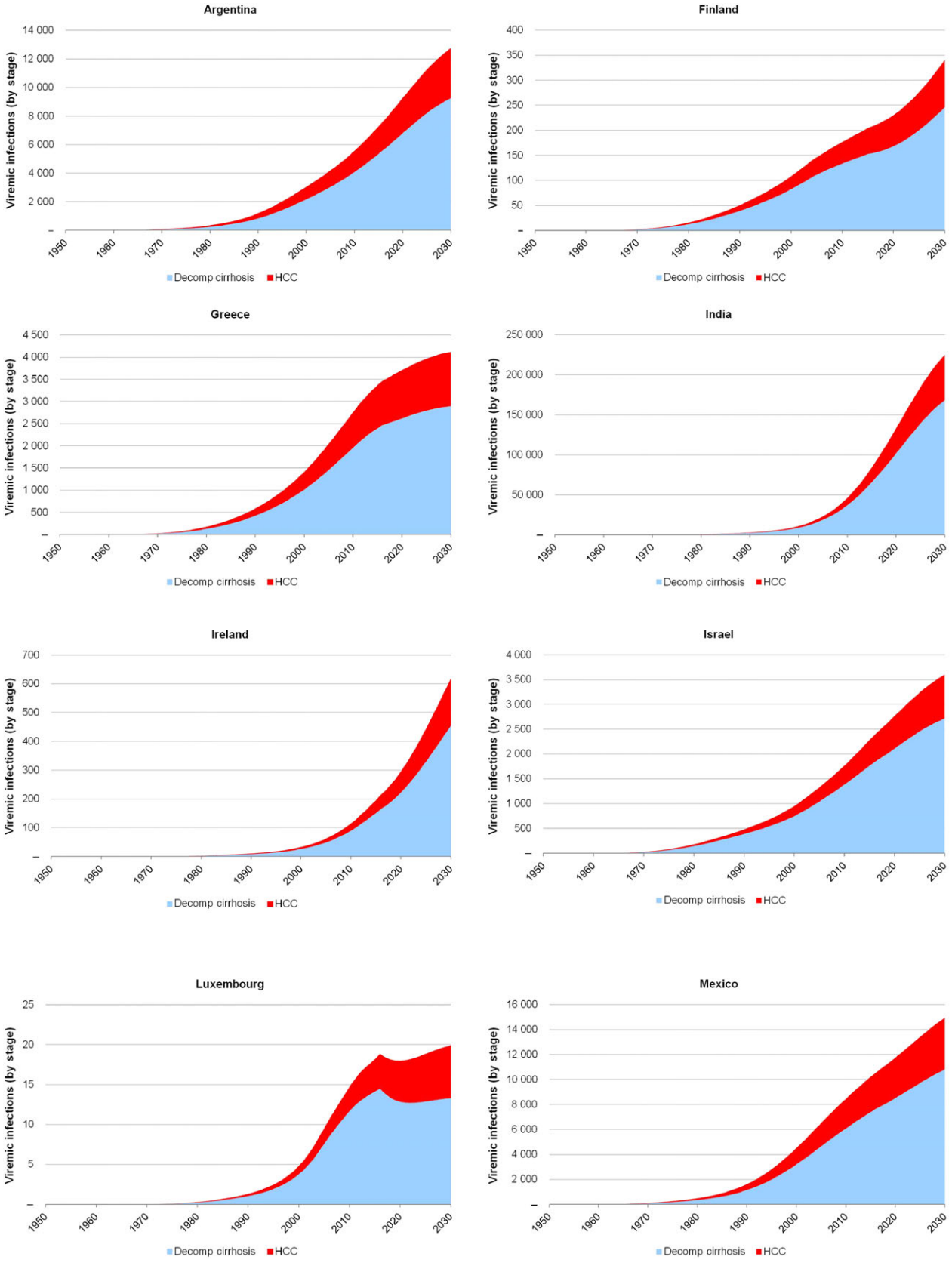

Fig. 5 Change in the number of liver transplants, decompensated cirrhosis cases and hepatocellular carcinoma (HCC) cases over time.

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Ireland

Expert consensus was used to estimate annual incidence. Transmission among IDU, MSM and new cases through immigration was considered. In 2013, it was estimated that there were 660 new cases in Ireland, based on 515 new infections occurring among IDU, 40 cases among MSM and 105 new cases due to immigration.

It is estimated that there are 30 300 (27 300–30 200) viremic individuals in 2013. Viremic infections are estimated to peak at 30 800 in 2020. In 2013, an estimated 3.7% of the viremic population experienced cirrhosis, HCC or liver transplant. By 2030, this proportion is projected to increase to 13.7%. The number of HCC and decompensated cirrhosis cases are projected to increase though 2030 when cases will number 160 and 190, respectively, more than doubling the 2013 values.

Israel

Based on expert consensus, the number of new HCV cases in Israel was estimated using an understanding of risk factors and immigration behaviour. Approximately 70% of new cases originated outside of the country [43], and waves in 1975 and 1990 are thought to have contributed significantly to the number of new cases of HCV. After 1990, cases dropped due to screening of the blood supply. In 2013, there were approximately 100 new cases occurring annually (1.3 cases per 100 000 persons).

It was estimated that there were 104 600 (41 500–108 200) viremic infections in 2013. Viremic infections were estimated to have peaked at 115 200 in 2005 and to decrease to 67 800 by 2030. From 2013 to 2030, liver-related mortality and HCC were projected to increase 80% and 90%, from 440 to 790 and from 460 to 880. Cirrhosis and decompensated cirrhosis were projected to increase 55% and 65%, respectively, from 10 400 and 1440 in 2013 to 16 120 and 2370 in 2030.

Luxembourg

The number of new infections began to increase in Luxembourg around 1970 and peaked in 1989 before blood supply screening began in 1990. The annual number of new infections in Luxembourg was estimated through an analysis of subpopulations and immigration. In 2012, it was estimated that 75 new infections resulted from IDU, 3 originated in prisons, 74 entered the country through immigration and 12 occurred among asylum seekers. After accounting for duplication (i.e., prisoners or immigrants who inject drugs), there were approximately 110 new infections in 2012.

It was estimated that there were 3080 (1940–3390) viremic infections in 2013. Viremic infections were estimated to have peaked at 3110 in 2010 and to decrease to 2780 by 2030. HCC was projected to increase 75% from 4 in 2013 to 7 in 2030. Additionally, from 2013 to 2030, liver related mortality was projected to increase 25% from 4 to 5 deaths annually. Decompensated cirrhosis was projected to peak in 2016 at 11 cases, before decreasing to 10 cases in 2030. Additionally, cirrhosis was projected to increase 30% from 90 cases in 2013 to 120 in 2030.

Mexico

With the majority of cases arising from transfusion prior to the implementation of blood screening protocol, the annual number of HCV infections was estimated to peak in the mid-1990s [45]. The annual number of new cases was estimated at 5620 new cases in 2013.

In 2013, the total number of viremic infections was estimated at 560 700 (326 900–605 200), and it was forecasted to decrease to 406 100 viremic infections in 2030. The number of HCC cases in 2013 was estimated at 2660 cases, and it was forecasted to increase by 55% by 2030. The number of liver related deaths will increase by 55% from a base of 2370, while decompensated cirrhosis and compensated cirrhosis infections will increase 55% and 40% from a base of 6750 and 54 460 in 2013.

Mongolia

Based on expert consensus, it was estimated that peak incidence occurred in 1970 and has since decreased. In 2013, there were an estimated 3030 new infections in Mongolia.

There were an estimated 200 000 (136 000–245 000) infected individuals in 2013. Prevalence is estimated to have peaked at 222 200 patients in 1995 and declines to 165 500 by 2030. There will be 27 500 compensated cirrhotic patients in 2030 as compared to 25 900 in 2013. In addition, there will be 1520 cases of HCC, and 4330 patients progressed to decompensated cirrhosis by 2030. Liver related deaths in 2030 will number 1400 as compared to 1130 deaths in 2013. In 2013, 15% of viremic cases are estimated to have compensated cirrhosis or more advanced liver disease (decompensated cirrhosis, HCC or transplant), while this proportion will increase to 20% in 2030.

The Netherlands

There are reliable data in the Netherlands estimating the number of adults living with an active HCV infection [49]. However, the exact number of new infections was difficult to quantify. It was estimated that the number of new infections peaked in 1989 and gradually declined thereafter. The epidemiology of HCV infection in the Netherlands is

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changing, with an increase in the number of people immigrating from low- and middle-income countries as well as the spread of HCV infection among HIV positive men having sex with men [49]. Traditional risk factors such as transfusion, IDU and nosocomial acquired infections have been reduced to nearly zero through quality prevention programmes. There were an estimated 510 new cases of HCV infections in the Netherlands in 2013, mainly related to immigration.

In 2013, the total number of active HCV infections was estimated at 20 000 (4700–36 500), and it was forecasted to decrease to 10 000 cases in 2030. The number of HCC cases was estimated to remain relatively constant at 90 annual cases due to the young age of the infected population. The number of liver related deaths in chronic HCV patients was forecasted to decrease by 25% from a base of 100, while decompensated cirrhosis and compensated cirrhosis will decrease by 45% and 40% from a base of 250 and 2270, respectively, in 2013.

New Zealand

Based on expert consensus, previous HCV modelling [57] and notification data [50], historical changes in incidence were estimated. It was estimated that peak incidence occurred in 1980 and has since decreased. In 2013, it is estimated that 1020 new infections occurred in New Zealand.

There were an estimated 50 000 (30 400–63 100) infected individuals in 2013. Prevalence peaked at 50 500 patients in 2010 and declines to 39 900 by 2030. There will be an estimated 330 HCV related deaths in 2030 as compared to 140 deaths in 2013. In 2013, 8% of viremic cases are estimated to have compensated cirrhosis or more advanced liver disease (decompensated cirrhosis, HCC or transplant), while this proportion will increase to 21% in 2030.

Norway

The annual number of new cases of HCV in Norway was estimated using expert consensus. HCV is thought to have peaked in 1980 due to an increase in IDU and to have decreased slowly due to sustained use. In 2013, there were an estimated 750 new cases occurring annually (14.9 cases per 10 000 persons).

It is estimated that there were 21 900 (15 200–26 900) viremic infections in 2013. Viremic infections were estimated to peak at 22 000 cases in 2018 before decreasing to 21 300 cases in 2030. HCC cases were projected to increase 115% through 2030 to 100 cases. Liver related mortality was expected to increase from 50 cases in 2013 to 80 cases in 2030, an 80% increase. Decompensated cirrhosis and cirrhosis cases were projected to increase 20% and 90%, respectively, from a base of 90 and 990 cases in 2013.

Poland

Data available on the number of new cases of HCV in Poland are based on a national reporting system carried out by National Institute of Public Health, and according to expert opinion are underestimated. The annual number of new cases is considered to have peaked in the mid-1990s to an estimated 5460 new cases in 2013.

In 2013, the total number of viremic infections was estimated at 200 000 (141 000–234 100) and was forecasted to decrease to 185 000 by 2030. The number of HCC cases in 2013 was estimated at 780 cases, and it was forecasted to increase by 50% by 2030. Similarly, the number of liver related deaths will increase by 50% from a base of 670, while decompensated cirrhosis and compensated cirrhosis infections will increase 40% and 30% from a base of 1580 and 16 000 in 2013.

Russia

The annual number of reported HCV infections in Russia is increasing [58]. The number of chronic HCV cases per 100 000 increased from 12.9 in 1999 to a peak of 40.9 in 2009. In 2012, there were 39.1 cases per 100 000 individuals. The annual number of new cases was estimated at 236 090 new cases in 2013.

In 2013, the total number of viremic infections was estimated at 4 525 800 (3 167 900–4 674 900), and it was forecasted to increase, with 6 163 500 viremic infections in 2030. The number of HCC cases in 2013 was estimated at 5170 cases, and it was forecasted to increase by 220% by 2030. The number of liver related deaths will increase by 215% from a base of 5110, while decompensated cirrhosis and compensated cirrhosis infections will increase 205% and 175% from a base of 17 140 and 145 330 in 2013.

Slovak Republic

There were limited data available on the number of new cases of HCV in the Slovak Republic. The annual number of new cases is considered to have peaked in the mid-1990s and declined thereafter. It was estimated that there were 760 new cases in 2013.

In 2013, the total number of viremic infections was estimated at 33 100 (21 900–41 300), and it was forecasted to decrease to 29 200 by 2030. The number of HCC cases in 2013 was estimated at 130 cases, and it was forecasted to increase by 50% by 2030. Similarly, the number of liver related deaths will increase by 40% from a base of 130, while decompensated cirrhosis and compensated cirrhosis

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infections will increase 30% from a base of 390 and 2900 in 2013.

South Africa

There were limited data available on the number of new infections. The contribution of blood transfusion is unclear, but is possibly low due to strict criteria for donation, screening for HCV using molecular methods and a lack of paid blood donation practices. Imported blood products prior to 1990 contributed to new cases of HCV in haemophiliacs. It is believed that immigration from other regions in Central and southern Africa and IDU will potentially lead to an increase in the incidence of HCV. The annual number of new cases was estimated at 6940 in 2013.

In 2013, the total number of viremic infections was estimated at 393 800 (238 000–475 000), and it was forecasted to decrease, with 219 000 viremic infections in 2030. The number of HCC cases in 2013 was estimated at 1610 cases, and it was forecasted to increase by 30% by 2030. The number of liver related deaths will increase by 30% from a base of 1550, while decompensated cirrhosis infections will increase 20% and compensated cirrhosis will remain flat from a base of 4810 and 39 700 in 2013.

DISCUSSION

A modelling approach was used to forecast HCV mortality and morbidity. As HCV disease burden changes over time, this approach allowed us to compare data across countries reported in different years [15] by estimating the disease burden in 2013 (Table 1). As shown in Fig. 3, the total number of viremic infections is expected to decline or remain flat in nearly all countries except for Russia, where the high incidence of new infections is anticipated to continue to grow the infected population. The total number of HCV infections reported here will be lower than those reported elsewhere, as this study focused on estimating the number of viremic cases in the population. Those who spontaneously cured the virus or were treated and cured were not considered. Figure 4 shows the change in disease burden over time, while Fig. 5 shows that the number of individuals with late-stage liver disease is expected to continue to grow in all countries except for the Netherlands and South Africa.

The Netherlands stands out as the only country where the future morbidity and mortality is projected to decrease from 2013 to 2030. The Netherlands already has a high treatment rate where 4.5% of the infected population is treated annually with current high SVR therapies (Table 1). This combination results in a reduction in HCV disease burden. If treatment rate is lowered to 1.5%, where 310 patients are treated annually between 2013 and 2030, liver related deaths, HCC, decompensated cirrhosis and cirrhotic HCV infections will actually increase by 45%, 60%, 21% and 21%, respectively, in 2013–2030. Thus, HCV disease burden can be managed through increased treatment rate if combined with high SVR therapies.

The number of individuals with advanced liver disease in South Africa is projected to drop after 2026 due to all-cause mortality. As shown in Fig. 2, South Africa has the oldest infected population among the countries studied. By 2026, the all-cause mortality is anticipated to result in a reduction in the total number of infections. This projection, however, is highly dependent on the accuracy of the age distribution estimate and the rate of new infections. As stated earlier, it was difficult to estimate the number of new HCV infections entering the country through illegal immigration. If the true number of new infections is higher than our estimates, the disease burden will continue to grow beyond 2030.

As shown in Table 1, viremic HCV prevalence ranged from 0.12% in the Netherlands to 3.17% in Russia, with the highest diagnosis rate represented by countries with a centralized registry (Finland, Ireland, Norway and Poland). India, Slovak Republic, South Africa and Poland were estimated to have the lowest diagnosis rate (range 5–15%), while Luxembourg, Finland, the Netherlands and Norway all had more than 55% of their infected population diagnosed. In addition, it was estimated that 0.6–5% of the infected population is newly diagnosed each year, with the lower end of the range represented by India and the upper end of the range represented by Norway. The Netherlands has the highest treatment rate, with 4.5% of the infected population treated annually. This was followed by Luxembourg at 3.2% and Norway at 2.8%. Of the countries studied, South Africa, Russia, Argentina and India all had treatment rates <0.5% (range 0.03–0.17%).

Mortality (all-cause and liver related) was driven by the age of the infected population (Fig. 2) as well as risk factors such as IDU and transfusion (Table 1). Older populations had a higher all-cause mortality rate [24] and in addition, disease progression rates increased with age. Thus, older individuals were more likely to have more advanced liver disease and associated liver related deaths. As stated in the methodology section, active IDU cases also had a higher mortality rate due to the high-risk behaviour associated with drug use. Table 1 presents the percentage of the infected population who were actively injecting drugs. The all-cause mortality was adjusted accordingly for this portion of the population.

In each country, details of the current treatment protocols were gathered. For the purpose of the model, it was assumed that all treatment assumptions (including the number of treated patients, treatment eligibility, the number of newly diagnosed cases, SVR and treated patient segments) would remain constant between now and 2030. This was not meant to be a realistic scenario, but was rather a baseline that could be used to compare the impact of new strategies to manage the future disease burden

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[59]. Thus, this work does not imply that the current treatment paradigm will remain as it is today. Instead, the scenarios shown here represent what would be the outcome if the current paradigm stayed the same.

Numerous limitations could influence the outcomes from this study. The model used the annual number of new cases and tracked their progression over time. As described earlier, distribution of new cases from 1950 to the year of available data was back-calculated using relative incidence and allocation of the new cases by age and gender. However, it was more difficult to estimate the number of new infections after the year of known prevalence. An analysis of the key risk factors was used to estimate the more recent number of new infections. Factors considered were new HCV infection among IDU, continued nosocomial infection and impact of immigration on the new cases of HCV. A key limitation of this study is the assumption that the number of new cases will remain constant after 2013. Higher numbers of new infections in 2013 could thus result in higher total numbers of infections in 2030.

A further limitation of this analysis is the assumption that sufficient numbers of diagnosed patients will be available for treatment. In reality, as the diagnosis rate increases, it will become more difficult to find undiagnosed patients. In addition, diagnosed patients may not have easy access to care. Thus, the ability of a country to treat its HCV population may be limited by the number of available diagnosed eligible patients.

In addition, the model does not consider the progression of cured HCV patients. Studies have shown that more advanced patients may continue their disease progression after achieving SVR, although at a slower rate [16]. The data presented here may overestimate the reduction in HCC and decompensated cirrhosis cases, as the scope of the analysis was limited to HCV viremic individuals. Another element not addressed by this model is the potential contribution of extrahepatic manifestations of HCV infection on all-cause mortality.

In conclusion, while the total number of HCV infections is expected to decline in many countries, HCV-related mortality and morbidity is expected to increase as the infected population ages and progresses to more advanced liver diseases. In all countries but the Netherlands, the HCV disease burden will not be controlled by the current treatment paradigm. Increased treatment and/or higher efficacy therapies are needed to keep the number of HCV individuals with advanced liver diseases and liver related deaths from increasing. This suggests that strategies are required to manage the expected increase in HCV disease burden.

ACKNOWLEDGEMENTS

This work represents the collaboration of many experts across numerous countries, and we are indebted to them all. We would like to thank J.E. van Steenbergen and Anna Krabbe-Lugnér of the National Institute of Public Health and Environment for all their contributions, review of the data and discussion of the Netherlands' analyses. We are grateful to Lelia Thornton (Health Protection Surveillance Center), Cathal Walsh and Jennifer Kieran of Trinity College in Dublin for providing data and validating our assumptions in Ireland. We are also thankful for the contributions of Markku Kuusi, Henrikki Brummer-Korvenkontio, Elisa Huovinen, Salla Toikkanen, Mikko Virtanen and Maarit Sillanpää of THL and Martti Färkkilä of Finland. They provided data and were involved in the discussion of national data that were used in this analysis. This project was supported by Gilead Sciences.

DISCLOSURES

A. Hatzakis has served as the co-chair of the Hepatitis B and C Public Policy Association funded by AbbVie, Bristol-Myers Squibb and Gilead. He has served also as speaker, consultant or advisor for AbbVie, BMS and Gilead. He has received grant support from AbbVie, Gilead and Novartis.

V. Chulanov has served as a speaker or advisor for AbbVie, Bristol-Myers Squbb, Gilead, Janssen, MSD and Novartis. He has received grant or research support from AbbVie, Bristol-Myers Squibb and Janssen.

A.C. Gadano has no conflict of interests.

C. Bergin has no conflict of interests.

Z. Ben-Ari has served as a speaker or advisor for AbbVie, Gilead, Bristol-Myers Squibb, Janssen, Boehringer Ingelheim, MSD and Roche.

J. Mossong has no conflict of interests.

I. Schréter has no conflict of interests. M.I. Andersson has received research support from Gilead, Roche and Alere. She has served on AbbVie advisory board.

O. Baatarkhuu has no conflict of interests.

S. Blach, C. Estes, E. Gower, H. Razavi and K. Razavi-Shearer have no conflict of interests. They are employees of The Center for Disease Analysis and are barred from accepting any personal consulting or any other outside funding. The Center for Disease Analysis has received research funding from public and private sources (Gilead Sciences, Boehringer Ingelheim and AbbVie), but its projects are limited to basic epidemiology and modelling research.

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R.J. de Knegt has served as a speaker or advisor for AbbVie, Bristol-Myers Squibb, Gilead, Roache, Merck and Norgine. He has participated in clinical trials or received research grants from AbbVie, Bristol-Myers Squibb, Gilead, Roche, Medtronic and Merck.

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C. Stedman has served as a speaker or advisor for Gilead Sciences, MSD, and Janssen.

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K. Tomasiewicz has served as a speaker or advisor for AbbVie, Bristol-Myers Squibb, Gilead, Janssen, MSD and Roche.

A.J. van der Meer has received financial compensation for lectures for Gilead and MSD.

F.R. Zuure has received financial support for the printing of her thesis from Gilead, Roche, MSD, AbbVie and Boehringer Ingelheim, and has worked on several research projects for which her institute received unrestricted grants from Gilead, Roche and MSD.

S. Acharya, I. Aho, A.C. Anand, V. Arendt, P. Arkkila, K. Barclay, F. Bessone, C.R. Brunton, G. Choudhuri, Y.A. Dahgwahdorj, O. Dalgard, J.R. Daruich, N.R. Dashdorj, D. Davaadorj, M. de Vree, C. Henderson, P. Hoffmann, J. Hornell, D. Houlihan, S. Hrusovsky, P. Jarčuška, D. Kershenobich, P. Kristian, Y. Lurie, A. Mahomed, N. Mendez-Sanchez, P. Nymadawa, M. Oltman, J. Oyunbileg, Ts. Oyunsuren, N. Prabdial-Sing, S. Radke, E. Ridruejo, R. Safadi, R. Sanduijav, V. Saraswat, C. Seguin-Devaux, S.R. Shah, I. Shestakova, A. Shevaldin, O. Shibolet, M.O. Silva, K. Souliotis, T. Staub, D. Struck, V. Sypsa, L. Undram, D. van Santen, I. Veldhuijzen, F.G. Villamil, S. Willemse, E. Zuckerman and P. Puri have no conflict of interests to declare.

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